Asparagine synthetase deficiency

Asparagine synthetase deficiency is a condition that causes neurological problems in affected individuals starting soon after birth. Most people with this condition have an unusually small head size (microcephaly) that worsens over time due to loss (atrophy) of brain tissue. They also have severe developmental delay that affects both mental and motor skills (psychomotor delay). Affected individuals cannot sit, crawl, or walk and are unable to communicate verbally or nonverbally. The few affected children who achieve developmental milestones often lose these skills over time (developmental regression).

Most individuals with asparagine synthetase deficiency have exaggerated reflexes (hyperreflexia) and weak muscle tone (hypotonia). The muscle problems worsen through childhood and lead to muscle stiffness, uncontrolled movements, and ultimately, paralysis of the arms and legs (spastic quadriplegia). Many affected individuals also have recurrent seizures (epilepsy). Not all affected people experience the same type of seizure. The most common types involve a loss of consciousness, muscle rigidity, and convulsions (tonic-clonic); involuntary muscle twitches (myoclonic); or abnormal muscle contraction (tonic). People with asparagine synthetase deficiency may have an exaggerated startle reaction (hyperekplexia) to unexpected stimuli. Some affected individuals have blindness due to impairment of the area of the brain responsible for processing vision, called the occipital cortex (cortical blindness).

People with asparagine synthetase deficiency typically do not survive past childhood.

Frequency

Asparagine synthetase deficiency is thought to be a rare condition. More than 20 affected individuals have been described in the medical literature.

Causes

Asparagine synthetase deficiency is caused by mutations in a gene called *ASNS*. This gene provides instructions for making an enzyme called asparagine synthetase. This enzyme is found in cells throughout the body, where it converts the protein building block (amino acid) aspartic acid to the amino acid asparagine.

In addition to being a component of proteins, asparagine helps to break down toxic ammonia within cells, is important for protein modification, and is needed for making a molecule that transmits signals in the brain (a neurotransmitter). Mutations in the *ASNS* gene that cause asparagine synthetase deficiency lead to a decrease or loss of functional enzyme. Asparagine from the diet likely makes up for the enzyme's inability to produce the amino acid in most cells. However, asparagine cannot cross the protective barrier that allows only certain substances to pass between blood vessels

and the brain (the blood-brain barrier). As a result, brain cells in people with asparagine synthetase deficiency have a shortage (deficiency) of this amino acid. The exact effect of asparagine synthetase deficiency on brain cells is unknown, but because of the severe features of this condition, it is clear that asparagine is necessary for normal brain development.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- ASNS deficiency
- ASNSD
- congenital microcephaly-severe encephalopathy-progressive cerebral atrophy syndrome
- disorder of asparagine metabolism

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Asparagine synthetase deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3809971/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22asparagine+synthetase+deficiency%22

Other Diagnosis and Management Resources

- GeneReview: Asparagine Synthetase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK525916

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Amino Acids
  https://medlineplus.gov/ency/article/002222.htm
- Health Topic: Amino Acid Metabolism Disorders
  https://medlineplus.gov/aminoacidmetabolismdisorders.html

Additional NIH Resources

- Eunice Kenney Shriver National Institute of Child Health and Human Development: Intellectual and Developmental Disabilities (IDDs): Condition Information
  https://www.nichd.nih.gov/health/topics/idds/conditioninfo/default
- National Institute of Neurological Disorders and Stroke: Epilepsy Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page

Educational Resources

- Centers for Disease Control and Prevention: Facts about Developmental Disabilities
  https://www.cdc.gov/ncbddd/developmentaldisabilities/facts.html
- Centers for Disease Control and Prevention: Facts about Microcephaly
  https://www.cdc.gov/ncbddd/birthdefects/microcephaly.html
- Kennedy Krieger Institute: Developmental Disorders
  https://www.kennedykrieger.org/patient-care/conditions/developmental-disorders
- MalaCards: asparagine synthetase deficiency
  https://www.malacards.org/card/asparagine_synthetase_deficiency
- March of Dimes: Amino Acid Metabolism Disorders
  https://www.marchofdimes.org/baby/amino-acid-metabolism-disorders.aspx
- Merck Manual Consumer Version: Overview of Amino Acid Metabolism Disorders
  https://www.merckmanuals.com/home/children-s-health-issues/hereditary-metabolic-disorders/overview-of-amino-acid-metabolism-disorders
- Orphanet: Congenital microcephaly-severe encephalopathy-progressive cerebral atrophy syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=391376

Patient Support and Advocacy Resources

- American Association on Intellectual and Developmental Disabilities (AAIDD)
  https://www.aaidd.org/
- American Epilepsy Society
  https://www.aesnet.org/

- Brain Foundation (Australia)
  https://brainfoundation.org.au/
- Citizens United for Research in Epilepsy (CURE)
  https://www.cureepilepsy.org/

Clinical Information from GeneReviews

- Asparagine Synthetase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK525916

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28asparagine+synthetase%5BTIAB%5D%29+AND+%28deficiency%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- ASPARAGINE SYNTHETASE DEFICIENCY
  http://omim.org/entry/615574

Medical Genetics Database from MedGen

- Asparagine synthetase deficiency
  https://www.ncbi.nlm.nih.gov/medgen/816301

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